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Brief Clinical Report

Type 3 Pfeiffer Syndrome With Normal Thumbs

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We report on a male infant with extremely shallow orbits, spontaneous luxation of the eyes out of the eyelids, hypoplastic midface, broad, medially rotated great toes, and respiratory distress due to severe bilateral posterior choanal stenosis. At 4 days he had open cranial sutures (both by palpation and radiological examination). Subsequent radiologic studies demonstrated: thickening of the skull base, vertebral anomalies, flattening of the olecranon fossae with dislocated radii, and triangular shape of the proximal phalanx of the first toes. Our patient had manifestations of type 3 Pfeiffer syndrome (PS). However, the finding of normal thumbs has not been reported in type 3 PS. Point mutations in fibroblast growth factor receptor-1 (FGFR1) and fibroblast growth factor receptor-2 (FGFR2) have been reported in familial and sporadic cases of PS, but were not found in this patient. Recognizing type 3 PS, despite variability in expression, is important for genetic counseling, prognosis, and decision-making regarding craniofacial surgery

KEY WORDS: acrocephalosyndactyly, Crouzon syndrome, Jackson-Weiss syndrome, Pfeiffer syndrome, proptosis, midface hypoplasia, skull base deformity, craniosynostosis, choanal stenosis

INTRODUCTION

We report on an infant with brachycephaly, midface hypoplasia, severe proptosis and abnormalities of the great toes consistent with the diagnosis of Pfeiffer syndrome (PS). However, the normal appearance of the thumb on clinical and radiological examination brings that diagnosis into question.

CLINICAL REPORT

The patient, a black male, was born to a 26-year-old G4P4 black mother and non-consanguineous 24-year-old black father. The mother reported an uneventful pregnancy. She delivered at 38 weeks (by dates and ultrasound) via spontaneous vaginal delivery. Apgar scores were 3 at 1 minute, 6 at 5 minutes, and 7 at 10 minutes. The infant was transferred to the neonatal intensive care unit at age 1 day for treatment of respiratory distress.

Physical examination at 3 days: length 50.5 cm (3rd centile), weight 3.58 kg (50th centile) [Tanner et al., 1965], and head circumference of 34 cm (50th centile) [Nellhaus, 1968]. The anterior fontanelle was open and measured 5 × 6 cm. The posterior fontanelle was open. The sagittal suture was open 1 cm in width. He had a high forehead with flat supraorbital ridges. Telecanthus was present. The inner canthi were 2 cm apart (> 50th centile), and the outer canthal distance was 7 cm (> 95th centile) [Merlob et al., 1984]. The orbits were extremely shallow. The eyes luxated when the child cried (Fig. 1). Palpebral fissures slanted downward. The midface was hypoplastic. The palate was narrow and highly arched. Choanal stenosis was present, bilaterally. The hands and thumbs were normal. The first toe of each foot deviated medially, was broad, and had square tips (Fig. 2). Chromosomes were normal (46,XY).

The patient was hospitalized for the first 4 months of life. Complications arose during treatment of the respiratory distress due to choanal stenosis, including sepsis and intracranial hemorrhages. The patient's prognosis was extremely poor at the time of discharge due to the extensive loss of brain parenchyma following the intracranial hemorrhages. He died at home shortly after discharge. An autopsy was not performed.

Paraffin-fixed tissue from a neurosurgical procedure was recently sent to the laboratory of Dr. Maximillian Muenke (The Children's Hospital of Philadelphia) for DNA analysis. Single strand confirmation polymor-

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Fig. 1. Extremely shallow orbits with spontaneous luxation of the right eye.

Fig. 2. Broad, medially deviated first toe with square tip.

phism (SSCP) did not reveal the point mutations in fibroblast growth factor-1 (FGFR1) or fibroblast growth factor receptor-2 (FGFR2) which have been found in some cases of familial and sporadic PS (personal communication with Dr. Muenke).

IMAGING EXAMINATIONS

Skull radiographs in the newborn period and at age 3 months (Fig. 3) showed shallow orbits, severe maxillary hypoplasia, and a dense skull base. The anterior

Fig. 3. Radiograph at 3 months demonstrates brachycephaly, a thick dense skull base, and severe maxillary hypoplasia. (Craniotomy defect secondary to surgical decompression of intracranial hemorrhage.)

fontanelle and cephalad coronal sutures were open. Flattened olecranon fossae with congenital dislocated radial heads and abnormally modelled ulnae were present bilaterally (Fig. 4A, B). Bones of the hands were normal (Fig. 5), but each great toe was angulated medially and the proximal phalanx of each toe was triangular in shape (Fig. 6).

Detailed, thin section computed tomography of the skull base performed at age 4 months showed severe bilateral posterior choanal stenosis, but no atresia. The deviation of the nasal septum to the right made the stenosis worse on that side. The lateral walls of the orbits were splayed and nearly horizontal (Fig. 7A). The orbits were extremely shallow. The globes were displaced anteriorly and laterally. The medial and lateral pterygoids were thick and dense, as was the entire skull base. The nasofrontal suture was very thick, and the metopic suture was sclerotic. The spheno-occipital synchondrosis was present and open (Fig. 7B). The left sphenofrontal synchondrosis was irregular in appearance and prematurely fused. The sphenoethmoidal synchondrosis was nearly obliterated, representing premature fusion (Fig. 7C). The base of the coronal sutures appeared sclerotic and prematurely fused.

DISCUSSION

Our patient had craniosynostosis, maxillary hypoplasia, and shallow orbits with subsequent proptosis (which might be more accurately called pseudoexophthalmos [Grove, 1979]). He also had abnormalities of the great toe similar to those found in Jackson-Weiss syndrome. Jackson-Weiss syndrome is an autosomal dominantly inherited condition of craniosynostosis, midfacial hypoplasia, and abnormalities of the feet; some affected individuals have broad great toes which deviate medially. However, severe proptosis has not been reported with the abnormalities of the great toe and normal thumbs found in the Jackson-Weiss syndrome [Cohen, 1986].

In a recent article, Cohen [1993] has reported a subtype of PS with manifestations similar to those of our patient. Type 3 PS is described as having severe ocular proptosis, an extremely short anterior cranial base, neurological compromise and a poor prognosis with early death. A photograph of one such patient (Fig. 8 in Cohen's article) shows a face that closely resembles that of our patient. Two other Type 3 PS patients, each with a similar face, race, and poor prognosis in infancy, have been reported [Alvarez et al., 1993; Barone et al., 1993]. All of these patients, including the one we are reporting, had choanal stenosis. Also, all reported cases of type 3 PS have been sporadic [Cohen and Barone, 1994].

Variability of findings, including elbow ankylosis, visceral anomalies and normal thumbs have been acknowledged. Elbow ankylosis and visceral anomalies were absent in our patient. Muenke et al. [1994] has reported a PS family in which some individuals have normal thumbs and a mutation in FGFR1 gene on 8p.

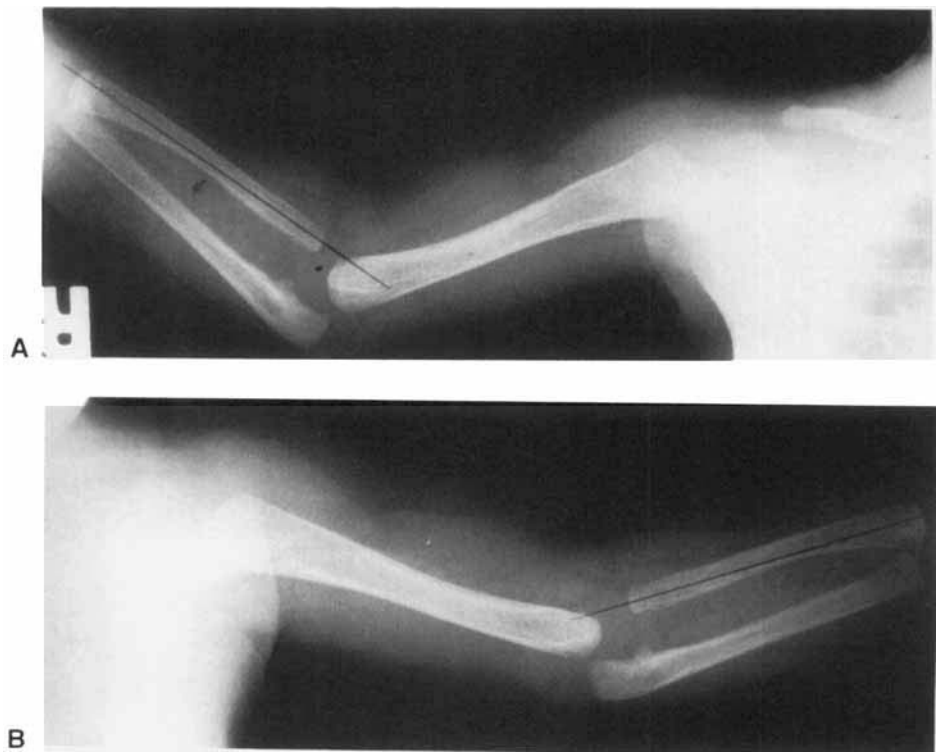

Fig. 4. **A**: Right upper limb radiograph, and (**B**) left upper limb radiograph demonstrating dislocation of the radial heads with abnormal ulnae and flattened olecranon fossae, bilaterally.

Fig. 5. AP radiograph of the left hand. Both thumbs were normal.

Fig. 6. AP radiograph of the left foot. Medial angulation of great toe with a triangulated proximal phalanx.

However, several of the relatives did have hand anomalies (symphalangism). Recently, patients with normal thumbs have been acknowledged as having PS, though discussion of the relationship between abnormal thumbs and the various types of PS was not undertaken [Cohen, 1995].

Not only is there phenotypic variability in PS and other acrocephalosyndactylies, but recent molecular data indicate variable phenotypic expression for patients with identical mutations. Linkage data has shown that a subset of PS families has a common mutation in the FGFR1 gene [Muenke et al., 1994]. However, point mutations in FGFR2 have been identified in Crouzon, Jackson-Weiss, and Apert syndromes, in addition to sporadic cases of PS [Schell et al., 1995; Rutland et al., 1995]. A possible explanation given by Rutland is that sporadic cases have sequence polymorphisms in another part of the same gene which can affect phenotypic expression of the same mutant allele. Cohen [1995] cautions that some of the patients reported by Rutland et al. [1995] were sporadic cases of Jackson-Weiss. Thus, even with molecular analysis, phenotypic variation still presents difficulties in diagnosing PS.

Our patient did not demonstrate the point mutations in FGFR1 or FGFR2. However, given the many similarities between our case and previously reported type 3 PS cases, we conclude that this case represents a variant of type 3 PS with normal hands and thumbs.

In addition to the question of syndromic classification, this case lends support to the theory that premature fusion of the anterior cranial base synchondroses, not cranial vault synostoses, is responsible for the orbit and midface anomalies seen in the craniosynostosis syndromes. The coronal sutures had started fusing at the base of the skull at age 4 months, but the cephalad portions were still open. Cranial base anomalies were present at birth.

It is probable that our patient would have progressed to a pancraniofacial synostosis, with closure of the cranial vault sutures and subsequent hydrocephalus. Early subtotal craniotomy and fronto-orbitofacial advancement has been advocated for this condition [Heeckt et al., 1993]. Furthermore, immediate tracheostomy and intracranial shunting are advocated for the airway and hydrocephalus problems in infants born with extensive skull base and cranial synostosis closure. Thus, it is important that type 3 PS be recognized before major operations are performed. After counseling as to the poor prognosis of these individuals, parents might opt to delay or avoid such procedures.

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Fig. 7. Thin section, 1.5 mm axial skull base computed tomography. **A**: Nearly horizontal lateral orbital walls, extremely shallow orbits, and lateral globe displacement. **B**: Open spheno-occipital synchondrosis (arrow). Note also dense, poorly aerated mastoids. **C**: Spheno-ethmoid sutures (small arrows) and both coronal sutures (large arrows) are prematurely fused.

gather patient materials for the preparation of the manuscript.

REFERENCES

Alvarez MP, Crespi PV, Shanske AL (1993): Natal molars in Pfeiffer syndrome type 3: A case report. J Clin Ped Dent 18:21–24.

Barone CM, Marion R, Shanske A, Argamaso RV, Shprintzen RJ (1993): Craniofacial, limb, and abdominal anomalies in a distinct syndrome: Relation to the spectrum of Pfeiffer syndrome type 3. Am J Med Genet 456:745–750.

Cohen MM (1986): Syndromes with craniosynostosis. In Cohen MM (ed): "Craniosynostosis." New York: Raven, pp 453–590.

Cohen MM (1993): Pfeiffer syndrome update, clinical subtypes, and guidelines for differential diagnosis. Am J Med Genet 45:300–307.

Cohen MM (1995): Craniosynostoses: Phenotypic/molecular correlations. Am J Med Genet 56:334–339.

Cohen MM, Barone CM (1994): Reply to Dr. Winter (letter, comment). Am J Med Genet 49:358–359.

Grove AS (1979): Orbital disease: Examination and diagnostic evaluation. Ophthalmology 86:854–863.

Heeckt P, Muchlbauer W, Anderl H, Schmidt A, Hopner F (1993): Early radical treatment of pancraniofacial synostosis. Ann Plast Surg 30:312–319.

Merlob P, Sivan Y, Reisner S (1984): Birth Defects: Original Article Series 20:1–51.

Muenke M, Schell U, Hehr A, Robin NH, Losken HW, Schinzel A, Pulleyn LJ, Rutland P, Reardon, W, Malcolm S, Winter RM (1994): A common mutation in the fibroblast growth factor receptor 1 gene in Pfeiffer syndrome. Nature Genet 8:269–274

Nellhaus, G (1968): Composite international and interracial graphs. Pediatrics 41:106.

Robin NH, Feldman GJ, Mitchell HF, Wilroy RS, Zackai EH, Allanson JE, Reich EW, Pfeiffer RA, Clarke LA, Warman ML, Mulliken JB, Brueton LA, Winter RM, Price RA, Gasser DL, Muenke M (1994): Linkage of Pfeiffer syndrome to chromosome 8 centromere and evidence for genetic hetrogenity, Hum Mol Genet 3:2153–2158

Rutland P, Pulleyn LJ, Reardon, W, Baraitser M, Hayward R, Jones B, Malcolm S, Winter RM, Oldridge M, Slaney SF, Poole MD, Wilkie AOM (1995): Identical mutations in the FGFR2 gene cause both Pfeiffer and Crouzon syndrome phenotypes. Nature Genet 9: 173–176.

Schell U, Hehr A, Feldman GH, Robin NH, Zackai, EH, de Die-Smulders C, Viskochil D, Stewart JM, Wolff G, Ohashi H, Price RA, Cohen MM, Muenke M (1995): Mutations in FGFR1 and FGFR2 cause familial and sporadic Pfeiffer syndrome. Hum Mol Genet 4:323–328.

Tanner JM, Whitehouse RH, Takaishi M (1965): Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. Arch Dis Child 41:613–635.